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Simple preparation of β-hydroxy-α-thiomethyl carbonyl compounds via stereoselective conjugate addition of thiol to Baylis–Hillman adducts

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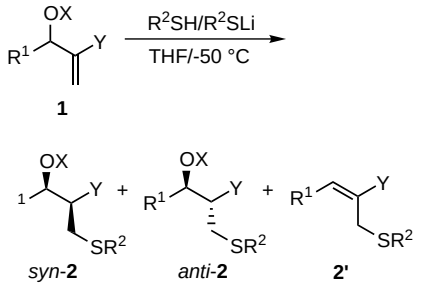
Abstract—Nucleophilic addition of thiols to Baylis–Hillman adducts smoothly proceeded in the presence of catalytic amounts of lithium thiolate to give *syn*-β-hydroxy-α-thiomethyl carbonyl compounds stereoselectively.

The aldol reaction is a most important organic reaction and numerous stereoselective or enantioselective methodologies have been developed so far.[1] Great success usually comes from the reaction promoted under Lewis acidic conditions so that dry conditions under inert gas atmosphere are usually required.[2] During the course of our study on the tandem Michael/aldol reaction, we were interested in the construction of β-hydroxy-α-thiomethyl carbonyl compounds.[3] The Baylis–Hillman reaction is recognized as a powerful tool for the preparation of β-hydroxy-α-methylene carbonyl compounds.[4] Although the reaction involves several drawbacks, it is undoubtedly useful because it can be performed in a large scale under air atmosphere regardless of dry conditions. Conjugate addition to Baylis–Hillman adducts generates intermediate enolates which, if the usual alkoxide elimination can be suppressed,[5] potentially provides a concise synthesis of substituted aldol adducts.[6,7] In this paper, we report a stereoselective method to prepare functionalized β-hydroxy-α-thiomethyl carbonyl compounds via conjugate addition of a thiol to a Baylis–Hillman adduct.

Treatment of derivatives of the Baylis–Hillman adducts with thiols resulted in the rapid disappearance of the starting material (Scheme 1). The results are summarized in Table 1.

Addition of thiophenol to **1a** in the presence of Et_3N afforded only the α,β-unsaturated ester **2′**, indicating a relatively facile ejection of acetate as the leaving group (entry 1). Changing the protective group to TBS led to a successful formation of the adduct **2b** in good yield (entry 2). Unfortunately, the isolated product contained about a 2:1 mixture of two diastereomers of **2b**. To improve the stereoselectivity, ethanethiol was used instead of thiophenol; the reaction was completed smoothly and *syn*-**2c** was isolated in 94% yield (entry 3).[8] HPLC analysis showed the *syn*/*anti* ratio of the mixture was 97/3. The high *syn*-selectivity was still observed in the reaction performed in wet-THF at room temperature (entry 4). Other Baylis–Hillman adducts also underwent selective conjugate addition to give *syn*-**2** in good yields (entries 6–9). The reaction conditions could be applied to ketone adducts of the Baylis–Hillman reaction (entry 10), but the selectivity was lost in the reaction of nitrile (entry 11).



Scheme 1.

Keywords: Baylis–Hillman reactions; Michael reactions; thiols; stereoselection; azetidinones.

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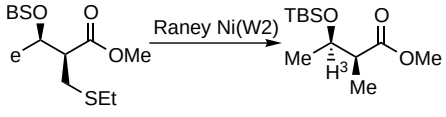
Table 1. Michael addition of thiols to Baylis–Hillman adducts **1**

Entry	Y	R^1	R^2	X	Temp (°C)	**2**; Yield (%)[a]	*syn*/*anti*[b]
1	CO_2Me	Me	Ph	Ac	−50	**2a**; 0[c]	–
2	CO_2Me	Me	Ph	TBS	−50	**2b**; 91	63/37
3	CO_2Me	Me	Et	TBS	−50	**2c**; 94	97/3
4	CO_2Me	Me	Et	TBS	rt	**2c**; 91	92/8
5	CO_2Me	Me	Et	H	−50	**2d**; 90	70/30
6	CO_2Bu-*t*	Me	Et	TBS	−50	**2e**; 83	92/8
7	CO_2Me	Et	Et	TBS	−50	**2f**; 78	94/6
8	CO_2Me	*i*-Pr	Et	TBS	−50	**2g**; 79	92/8
9	CO_2Me	*p*-Cl-C_6H_4-	Et	TBS	−50	**2h**; 95	99/1
10	COMe	Me	Et	TBS	−50	**2i**; 60	90/10
11	CN	Me	Et	TBS	−50	**2j**; 85	54/46

[a] Isolated yield.
[b] Determined by HPLC analyses.
[c] Et_3N was used as a base. S_N2' product was formed quantitatively.

The stereochemistry of the adduct was determined by comparison of the NMR data for known compounds after the desulfurization reaction (Scheme 2). Compound **2c**, for example, was treated with Raney-Ni (W2) to give known *O*-silylated aldol **3** in 73% yield. Comparison of the chemical shifts for two methyl groups and the H^3 proton with the reported data indicated that the compound had *syn*-configuration.[9]

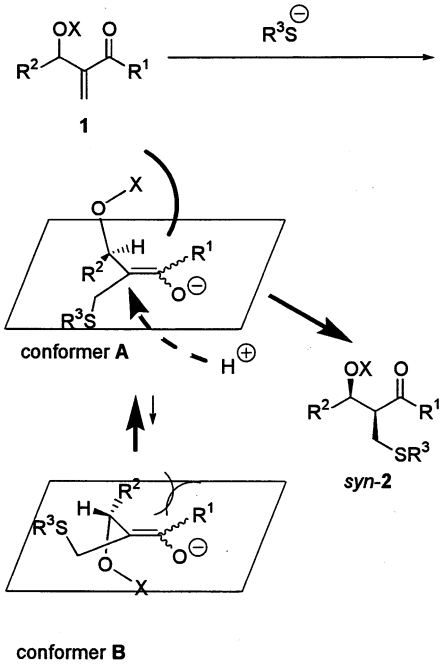
The plausible origin of the stereoselectivity is depicted in Scheme 3. The addition starts with the nucleophilic attack of the thiolate anion to **1** to give the enolate anion intermediate, in which two conformers **A** and **B** exist.[10] Due to steric interaction between the enolate residue and the R^2 group, conformer **A** should be favorable. The top face of **A** is likely shielded by the bulky TBSO group so that the protonation occurred from the bottom side of **A** to give *syn*-**2** stereoselectively. If a very bulky thiol such as thiophenol is used, the R^3S group likely shields the bottom face in **A** so that either side of **A** will be disfavored for the protonation. As a result, the difference between them should be small and the selectivity is lost (Table 1, entry 2). Absence of the TBS group makes the steric size of the shielding group small and the level of the stereoselection becomes modest (Table 1, entry 5). Ketone derivatives should proceed through a similar mechanism (Table 1, entry 10), but for the reaction with nitrile, due to its straight structure, the difference between **A** and **B** should be lost and the reaction takes place non-selectively.



syn-**2c** **3**; 73%

δ (ppm):
1.14, 1.16 for two Me groups (lit. 1.13, 1.14)
4.09 for H^3 (lit. 4.07)

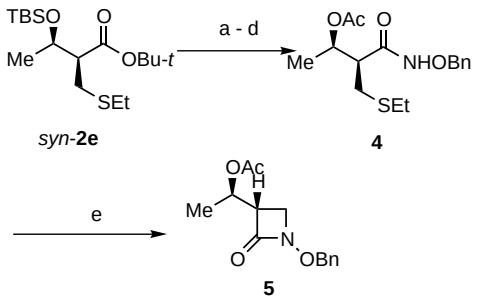
Scheme 2.



Scheme 3.

Conversion of the adduct **2** to β-lactam was attempted (Scheme 4). Acidic hydrolysis of *syn*-**2e** and subsequent condensation with NH_2OBn, for example, gave amide **4** that was smoothly converted to β-lactam **5** in diastereomerically pure form through the formation of sulfonium salt followed by intramolecular S_N2 reaction.[11]

Due to the wide applicability of the Baylis–Hillman reaction, the present procedure will provide a useful preparation of *syn*-aldol adducts of ester or ketone. It should be noted that the high stereoselectivity and the yield were achieved in wet-THF conditions at room temperature. Use of the thio-functionality also opens a new aspect of the adduct in synthetic use. Further application of this methodology is now underway in our laboratory.



Scheme 4. *Reagents and conditions*: (a) TBAF, 99%; (b) Ac_2O, DMAP, 87%; (c) TsOH (10 mol%), wet benzene, reflux, 93%; (d) EDCI, NH_2OBn, 84%; (e) $AgClO_4$, MeI, then K_2CO_3, 64%

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8. **Preparation of 2c.** To a solution of EtSH (0.32 mL, 4.32 mmol) in dry THF (distilled over potassium-benzophenone ketyl, 15 mL) was added BuLi (1.6 M, 0.25 mL, 0.40 mmol) at −50°C. Methyl 2-[1-(*tert*-butyldimethylsilyloxy)ethyl]acrylate (0.923 g, 3.78 mmol) was added to the solution at −50°C, and the resulting reaction mixture was allowed to stir at the same temperature for 15 h. HCl aq. (1 M, 40 mL) was added to the mixture and the organic phase was separated. The water phase was extracted with EtOAc (3×70 mL) and the combined organic phase was dried over Na_2SO_4. After filtration, the organic solvent was removed in vacuo and the residue was purified through flash chromatography (hexane then hexane/ether 30:1 v/v) to give adduct **2c** in 94% yield (1.08 g, 3.54 mmol). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.16 (d, 3H, J=6.3 Hz), 1.24 (t, 3H, J=7.2 Hz), 2.53 (q, 2H, J=7.2 Hz), 2.62 (ddd, 1H, J=3.5, 6.9, 10.2 Hz), 2.71 (dd, 1H, J=10.6, 12.5 Hz), 2.86 (dd, 1H, J=3.6, 12.5 Hz), 3.71 (s, 3H), 3.98 (quint, 1H, J=6.3 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.8, −4.1, 14.8, 18.1, 22.2, 25.9, 26.3, 30.2, 51.8, 55.0, 69.4, 173.7. Anal. calcd for $C_{14}H_{30}O_3SSi$: C, 54.85; H, 9.86. Found: C, 54.58; H, 9.89.
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